

REVIEW ARTICLE

Neoadjuvant chemoradiotherapy in rectal cancer and anorectal sphincter dysfunction: Review of the literature

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Summary

Purpose: The purpose of this article was to review the current medical literature regarding deterioration of anorectal function in patients receiving neoadjuvant chemoradiotherapy before surgery for locally advanced rectal cancer.

Methods: We reviewed the current literature including research studies, electronic database PUBMED-MEDLINE, published research results and metanalysis papers from high-volume institutes, collecting and comparing the different results. Pathophysiology as well as emerging solutions for treating anorectal sphincter dysfunction were researched in order to provide an insight of this complex issue.

Results: All available data suggest that neoadjuvant radiation therapy impairs internal anal sphincter function mostly

through nerve damaging mechanisms, as nerves are more susceptible to damage than muscular fibers.

Conclusion: Current radiotherapy recommendations are oriented in exclusion of anal canal from radiation field when oncologically safe or using new sphincter-sparing techniques for neoadjuvant radiotherapy aiming to improve the patient quality of life receiving radiation therapy prior to surgery. However, more well designed studies are required to assess the pathophysiology as well as treatment options for this complex matter, which strongly affects the quality of life of rectal cancer patients.

Key words: anorectal, cancer, chemoradiotherapy, neoadjuvant, sphincter, therapy

Introduction

Colorectal cancer (CRC) is the fourth most common cause of death from malignancy [1]. The most important prognostic factor for overall survival rate is the TNM stage, lymph node invasion, vascular invasion, histopathological type and resection margin status. These factors are the main parameters taken into account for optimizing the treatment plan for every patient. Preoperative chemoradiotherapy has been recommended as the standard treatment for locally advanced cancer of the middle and low third of the rectum. Well proven benefits are reduction of the tumor mass, block tu-

mor invasion, increase of the tumor resection rate and reduction of local recurrence rates.

Nowadays, rectal cancer patients staged preoperatively [2] as T3N0 or T1-3N1-2, receive neoadjuvant chemoradiotherapy. This includes long-term preoperative radiotherapy (5-6 weeks), or long-term preoperative concurrent chemoradiotherapy or short-term preoperative radiotherapy of approximately 5 days [3]. Regarding neoadjuvant chemotherapy capecitabine is an acceptable alternative to infusion 5-Fluorouracil in patients who are able to manage the responsibilities in self-administered

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oral chemotherapy. However, concurrent administration of Oxaliplatin and radiotherapy is currently not recommended [2].

The recommended radiation dose according to the National Comprehensive Cancer Network (NCCN) guideline is 45-50Gy in 25-28 fractions using multiple radiation fields. The treatment period for neoadjuvant chemoradiotherapy is about 5-6 weeks followed by 5-10 weeks interval, after which surgery is performed, following a new estimation of invasion depth (T stage), number of metastatic lymph nodes (N stage), and infiltration of mesorectal fascia-MRF [9]. Despite the above mentioned benefits of neoadjuvant radiotherapy, troublesome side effects may occur that can seriously affect the quality of life for these patients. The most distressful and common problem is anal sphincter dysfunction. It can manifest either as a solitary entity or as part of the low anterior resection syndrome (LARS), a syndrome representing a constellation of symptoms that patients experience in regard to their bowel habits post-low anterior resection operations. Fecal incontinence can be encountered commonly as part of this syndrome and it is the main target of this review.

Methods

We reviewed the current literature including research studies in PUBMED/MEDLINE, published research results and metaanalysis papers.

Results

Neoadjuvant therapy (NT) for resectable rectal cancer successfully reduces the risk of local recurrence significantly [5]. Unfortunately, NT is accompanied with an aggravation of anorectal function in many patients. Long-term evaluations of randomised trials have demonstrated an almost two-fold higher prevalence of bowel dysfunction in patients undergoing both surgery and preoperative short-course radiotherapy compared to patients undergoing surgery alone [6-9]. The reason for the additional impairment of functional outcome after NT remains unknown and despite the fact that many research centers have tried to precisely document and explain the underlying pathophysiology there is still no scientifically satisfying explanation. In an interesting study from an Australian radiotherapy group [10], including patients with prostate malignancy and not rectal cancer, using however the same as for rectal cancer radiation treatment plan as for any pelvic malignancy, showed that in 35 patients who received pelvic irradiation of 55 Gy in a period of 4-6 weeks, there

were 45% and 23% of patients respectively that presented with symptoms such as the urgency of defecation and fecal incontinence. Additionally internal anal sphincter and/or external anal sphincter were all proved damaged through resting (normal) anal pressure and full load (squeeze) anal pressure compared to baseline. The damage mechanism was not fully understood and electromyography of anal sphincters did not demonstrate abnormal nerve conduction signal, so incontinence was attributed to damage of the muscle itself from the catastrophic effect of radiation and post-radiation fibrosis. Therefore, the authors of this study [10] conclude that appropriate radiotherapy protocols, dosage and the radiation field should be carefully reviewed and implemented [11]. More recent radiotherapy trends of three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) can reduce the actual received dose of anal sphincter without compromising the radiotherapy effect [12]. The key point is to clearly contour the anal sphincter continuously in each slides of CT images and restrict the dose of anal sphincter through lead blocking. This method can reduce the received dose from original 33Gy to 6Gy. For a certain portion of irradiation fields which include the anal sphincter and distal rectum, the dose should also be limited to 40-45Gy [13]. Furthermore, for preoperative radiotherapy, IMRT was introduced in order to reduce the radiation-associated toxicities by decreasing the volume of high irradiation dose of surrounding normal tissues, compared to conventional radiotherapy or 3DCRT [14]. IMRT allows higher radiation doses to be focused on tumor, while minimizing the dose directed to surrounding normal critical structures compared to conventional 3D and 2D techniques. It was successfully documented by Hartley's meta-analysis [15] who reviewed a total of 3157 rectal cancer patients, that IMRT may provide a potential to increase treatment dose aiming to improving tumor response and decrease the dose delivered to normal structures [16].

Discussion

Several studies using questionnaires, clinical examination and anorectal physiological testing in patients treated for rectal cancer have suggested that pelvic irradiation impairs anorectal function severely [17-21]. However, the evidence for the functional consequences of pelvic irradiation on anal sphincters has been indirect and incomplete, based only on clinical and manometric parameters. Most of the studies in the current literature lack uniformity and are a mixture of various target or-

gans, pre-post operative treatments, different radiation techniques and doses received by anal sphincters [22, 23]. Additionally, due to the well known fact that surgery alone affects anorectal function of patients treated for rectal cancer, it is challenging to quantify to which extent the damage is caused by surgery or pre-op pelvic irradiation. Furthermore, the identification of these mechanisms of damage will provide knowledge that will aid in preventing the damage caused by any factor. A recent study performed by Oxford University and University of Sienna in Italy [24] provided a physiological basis for chemoradiotherapy (CRT)-induced impairment of internal anal sphincter function (IAS) in patients treated for rectal cancer. The study was performed *in vitro* and samples of the internal anal sphincter were collected from patients undergoing abdominoperineal resection. A group of patients was treated by surgery alone (control group) and the other group received preoperative chemoradiotherapy (treatment group). Sphincter strips were mounted in a specific solution bath and the responses to electrical field stimulation and drugs were monitored and calculated. More specifically the intrinsic nerves seemed to be more susceptible to radiation injury than smooth muscle, although muscular damage also occurred. This study clearly showed that CRT adversely affects the function of IAS in patients treated for rectal cancer and provided comparison and an important theoretical basis proving specific histological alterations. Only a new recent study by Bregendhall and Emmertsen [25] investigated the pathophysiological effect of neoadjuvant therapy (NT) in patients with major low anterior resection syndrome (LARS) after total mesorectal excision (TME) surgery and compared it with the influence of NT in anal sphincters. In a retrospective manner, they studied the biomechanical wall properties, as well as anal sphincter function in patients treated with NT prior to resection, and compared them to a group of previously studied patients treated with resection only. In this explorative study it was documented that administration of NT leads to a severe impairment in neorectal sensitivity and an altered perception of defecatory urge among patients with major LARS after TME surgery for rectal cancer [26]. In addition, more NT patients reported that bowel dysfunction affected their quality of life compared to non-NT patients (58 vs. 26%). The authors concluded that, despite similar symptom profiles, functional deterioration after NT may reside in different mechanisms than the effect of surgery itself. According to another interesting study after TME, the reformed neorectum has altered functional properties compared to the natural rectum, and a change in biomechanical

properties and sensation was to be expected [27]. Moreover, it is suggested that distension and hereby stimulation of defecatory urge is transmitted not only by receptors in the rectal wall but also by receptors in the pelvic fascia and the pelvic floor muscles. This may explain the fact, that the vast majority of the included NT patients had a preserved perception of rectal filling and defecatory urge in response to thermal and mechanical stimulation, and that altered sensibility did not seem to play a role in the pathophysiology of LARS in NT patients [25]. By contrast, radiation-induced fibrous changes of the neorectal surrounding tissues may have compromised the integrity of afferent neuronal pathways in NT patients, causing impairment in sensation and perception of thermal and mechanical stimuli observed in these patients. They were less able to perceive and prepare for timely defecation and as a result such sensory dysfunction could lead to symptoms of incontinence. In the study [27] reduced anal resting pressures, but similar anal squeeze pressures were documented when comparing NT+ patients to NT- patients. Reduced anal resting pressure is a common finding after pelvic radiotherapy, implying IAS muscle weakness. By contrast, the external anal sphincter (EAS) is more resistant to ionising radiation than the internal sphincter, which is reflected in the finding of reduced anal squeeze pressures following adjuvant radiotherapy [28, 29]. Compromised muscle integrity and impaired innervation are responsible for radiation-induced injury to IAS, which often leads to incontinence. In another study, Pollack et al [8] used endorectal ultrasonography (ERUS) and found more scarring of the anal sphincters in irradiated patients, who also presented with more symptoms of incontinence and frequency compared to non-irradiated patients.

Based on the above reports there has been an increasing focus on preventive strategies for excluding the anal canal and sphincters from the high-dose radiation field. Knowledge on the precise mechanisms responsible for functional impairment following neoadjuvant radiotherapy is important in the continuing re-evaluation of the current planning volumes for rectal cancer towards smaller, more tailored field sizes in order to reduce normal tissue toxicity. Unfortunately there is a growing number of studies in MEDLINE/PUBMED that have described different physiological implications of rectal resection, suggesting a multifactorial cause of LARS but only a few studies that have primarily investigated the influence of radiotherapy on anal sphincter function [20-30]. Anorectal dysfunctions after pelvic radiotherapy have been shown to be mostly dose-dependent [7] and the use of sphincter

shielding techniques may reduce the risk of anorectal complaints after NT for rectal cancer.

The main treatment of anal incontinence is conservative. There is a step up process according to the results and the process of success of the treatment. Conservative modalities for the treatment of anal incontinence include:

- I. Lifestyle modifications (cessation of smoking, weight loss).
- II. Dietary strategies (sodium and protein reduction, caffeine restriction, elimination of aggravating foods, fiber supplementation insolubles, adequate fluid intake, exercise, mechanical barriers- the anal plug).
- III. Medications (anti-diarrheal treatments).
- IV. Physical therapies (pelvic floor muscle training).

In many patients who experience anal incontinence the best result can be observed from the combination of any of these modalities [31]. The advice for patients usually is to start with lifestyle modifications. The effects of this management can be successful in more than one third of anal incontinence patients [32]. If the above strategies are unsuccessful, then dietary strategies can be applied and sometimes can be individualized with the help of specialized clinical dieticians. However, many patients experience better results with the use of anal plugs. There are two studies that compared the use of anal plugs with standard treatment [33, 34]. Patients that chose a plug device achieved anal continence in 37%, although there was poor compliance concerning plug use. Additionally, a systematic review showed that plugs may be helpful

in alleviating the problem of incontinence as long as they tolerated them and that patients persisted with their use [35]. Regarding medical therapies of incontinence there is an analysis of 13 studies that assessed the effects of medications such as loperamide, codeine, diphenoxylate (antidiarrheal therapy) on anal incontinence which found them effective in terms of continence outcomes in relation to placebo [36]. Finally, there is a number of patients that respond well to physical therapies such as sphincter exercises biofeedback therapy and electric stimulation. These modalities are indicated for patients who do not respond to other conservative measures [37, 38]. Unfortunately, the literature remains unclear on those treatments rationale and success rates, because they are not standardized.

In conclusion, pelvic radiotherapy causes neo-rectal hyposensitivity in patients receiving NT prior to TME surgery for rectal cancer, possibly due to impaired afferent nerve function. Combined with a weakened internal anal sphincter, the physiological changes in visceral sensory function may play a role in the pathogenesis of the additional bowel dysfunction observed following neoadjuvant radiotherapy [15]. More well-designed studies are required to assess pathophysiology as well as treatment options for this complex issue, which strongly affects the quality of life of rectal cancer patients.

Conflict of interests

The authors declare no conflict of interests.

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